REMARKS

Status of the Claims

Claims 26, 40, 41 43, 57 and 60 are currently amended.

Claim 37 is withdrawn.

Claims 1-25, 27-34, 38, 39, 44-56, and 62 are cancelled.

Claim 64 is newly added.

Claims 26, 35-37, 40-43, 57-61, 63 and 64 are pending examination in this application.

Claim Amendments

Claim 26 has been amended by:

reciting --patient-- rather than "mammal";

limiting the sample fluids to --brain extract or cerebrospinal fluid--;

incorporating the β-amyloids specified in claim 34;

reciting the control as "known not to suffer from the disease;" and

incorporating in step (c) that increased levels of β-amyloid in the sample as compared to the controls leads to the result stated in the preamble. No new matter has been incorporated in the claim, and all the amendments find written description support in the specification. All these amendments were made at the helpful suggestions of the examiners during the interview of 13 June 2007.

The amendments to claims 40, 41, 43 and 57 were made to secure proper dependency from claim 26. New claim 64 was added to specify a disease which is a precondition leading to Alzheimer's disease. Support for mild cognitive impairment (MCI) is found in the specification pages 4, 58-59, 73 and 74.

Interview Summary

Applicants wish to thank both Examiners Hayes and Wang for the courtesies they extended in the interview of 13 June 2007. The focus of the interview was to discuss the enabling support for the claimed invention drawn to determining whether a patient is susceptible to or at risk of a disease associated with β-amyloid formation by detecting the presence of β-amyloid 42 variant Aβ(2-42), Aβ(3-42), Aβ(4-42), Aβ(5-42), Aβ(6-42), Aβ(7-42), Aβ(8-42), or Aβ(9-42) in a sample of brain extract or cerebrospinal fluid. During the interview, Dr. Eugeen Vanmechelen went through his declaration and provided additional discussion on the background of the neuropathology of Alzheimer's disease. The examiners provided helpful suggestions for certain claim amendments that would overcome the pending claim rejections.

The first suggestion was to change the recitation of "mammal" to --patient--. Claim 26 has been so amended. Support for the amendment is found throughout the specification. *See e.g.* Specification pp. 52- 59.

The second suggestion was to limit the sample to cerebrospinal fluid or brain extract. Claim 26 has been so amended. Support for the amendment is found throughout the specification, in particular pp. 52-59, and Tables 6-8.

The third suggestion was to incorporate the specific Aβ variants from claim 34 into claim 26. Claim 26 has been so amended to recite the specific β-amyloid 42 variants Aβ(2-42), Aβ(3-42), Aβ(4-42), Aβ(5-42), Aβ(6-42), Aβ(7-42), Aβ(8-42), or Aβ(9-42) all of which demonstrate a positive correlation with the detection of a disease associated with β-amyloid formation and/or aggregation. *See e.g.,* Specification Table 8 and Rule 132 Declaration of Dr. Eugeen Vanmechelen, Appendix 3.

The fourth suggestion was to modify the recitation of the control to recite "known not to suffer from said disease." Claim 26 has been so amended.

The fifth suggestion was to incorporate in method step c the limitation of the increased level of the Aβ variant over that found in a control sample from a patient known not to suffer from the disease. This suggestion was made in order to have the result step match the preamble. This amendment to claim 26 has been made. Support for this amendment is found in the Specification, Examples 3 and 4, Figure 7 and Tables 6 and 8.

As a sixth suggestion, the examiners requested a copy of Braak E, et al., "Neuropathology of Alzheimer's Disease: What Is New Since A. Alzheimer?" *Clin. Neuroscience* (1999) 249: 14-22. During the interview, Dr. Vanmechelen referred to this article in support of his contention that S0 control (as referenced in Tables 6 and 8) is a person with out clinical symptoms of Alzheimer's disease but yet may suffer from preclinical or infraclinical stages of Alzheimer's disease, *i.e.,* a false negative control. Applicants supply with this response a copy of the Braak et al. article in a Second Supplemental Information Disclosure Statement and a Supplemental Rule 132 Declaration of Dr. Eugeen Vanmechelen detailing the false negative control position.

Claim Rejections for Lack of Enablement

Claims 26, 34-36, 40-43, 56-61 and 63 were rejected as failing to comply with the enablement requirement. Specifically, the Examiner stated that "the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." (Office Action mailed May 15, 2007, p. 3).

The present invention relates to a method for the early detection of N-terminal truncated forms of β-amyloid in patients, which aids in the determination of whether the patient may be susceptible to or at risk of diseases associated with β-amyloid formation and/or aggregation such as Alzheimer's disease. The specification teaches how to detect and identify N-terminal truncated and post-translationally modified $A\beta_{42}$ variants in dead subjects and living persons and determine whether said patient is at risk for or susceptible to a disease associated with β-amyloid formation and/or aggregation. In compliance with the enablement provision of 35 USC §112, Claim 26 has been amended to recite the specific $A\beta_{42}$ variants (i.e. Aβ(2-42), Aβ(3-42), Aβ(4-42), Aβ(5-42), Aβ(6-42), Aβ(7-42), Aβ(8-42), and Aβ(9-42)) which when detected in a patient's cerebrospinal fluid or brain extract support the determination that said patient is susceptible to or at risk of a disease associated with β-amyloid formation.

The examiner has acknowledged that the specification enables the detection of variants Aβ(5-42), Aβ(2-42), or other variants in CSF of patients with AD. (Office Action mailed May 15, 2007, page 4). Claim 26 has been amended to conform to the Aβ variants Aβ(2-42), Aβ(3-42), Aβ(4-42), Aβ(5-42), Aβ(6-42), Aβ(7-42), Aβ(8-42), and Aβ(9-42) which positively correlate with the detection of a disease associated with β-amyloid formation and/or aggregation. *See e.g.,* Specification Table 8 and Rule 132 Declaration of Dr. Eugeen Vanmechelen, Appendix 3. Further claim 26 has been amended to read on CSF and brain extract samples, which the examiner has acknowledged are enabled by the disclosure.

Applicant has shown that the claimed N-terminal truncated and post-translationally modified $A\beta_{42}$ variants comprise a significant amount of the β-amyloid plaques from the brains of both an infraclinical AD patient (Specification, Fig. 3), and a patient with full blown AD (Specification, Fig. 2 and Table 3). Further, Applicant has demonstrated the presence of N-

terminal truncated $A\beta_{42}$ peptides in the CSF of living patients with various stages of AD pathology (Specification, Table 8). Alzheimer's disease is a disease "associated with β-amyloid formation and/or aggregation," as recited in amended Claim 26. A skilled practitioner recognizes that the claimed invention relates to other diseases that result from or are characterized by β-amyloid formation and/or aggregation. Thus, Applicant's disclosure is sufficient to enable practitioner's to use the specified N-terminally truncated/post-translationally modified $A\beta_{42}$ peptides as an aid to determine whether a patient is susceptible to any disease associated with β-amyloid formation/aggregation as recited in the claims.

The Examiner agrees that Applicant has shown that Aβ8-42, Aβ2-42, Aβ3-42, Aβ4-42, Aβ5-42, Aβ6-42, Aβ7-42 and Aβ9-42 are relevant to AD. The Examiner's enablement rejection regarding Aβ8-42, however, is based on the reasoning that "[s]ince certain forms of Aβ42, such as Aβ8-42, Aβ11-42, Aβ10-42 variants, can also be detected in controls, they do not distinguish between the controls and AD" (Office Action mailed May 15, 2007, p. 4). As described below and evidenced by the current specification, the Rule 132 Declaration of Dr. Eugeen Vanmechelen and the Supplemental Rule 132 Declaration of Dr. Eugeen Vanmechelen, the detection of Aβ8-42 variant in a sample from a subject designated as 'S0 control' is consistent with the claimed invention and does not evidence a failure to distinguish between a control and a disease state.

As described by Dr. Vanmechelen, the term "control" is used differently in different portions of the specification, and detection of N-terminal truncated Aβ peptides in subjects designated as "control" subjects is consistent with the claimed invention. Possible confusion results from the use of the term "control." There are two well-defined classes of "control" patients—some which have preclinical AD pathology (but no clinical symptoms) and others that have no AD pathology (normal aging controls).

In the data presented in Figure 7, Table 6 and Table 8 there appears to be anomaly in that Aβ 8-42 is present in one of the control CSF samples (Control no. 148, Cru). As discussed in the Supplemental Rule 132 Declaration of Dr. Eugeen Vanmechelen at ¶¶ 10-11 this sample labelled as "control" is in fact a false negative control. In other words, this false negative "control" is a patient who did not exhibit any clinical symptoms of AD, but indeed was suffering from pathological changes. Detection of the indicated N-terminal truncated Aβ 8-42 peptides in this "control" is significant because this patient might be in either the preclinical or infraclinical stages of Alzheimer's disease; that is, where a combination of tau pathology and clinical assessment may not signal the subject's risk or susceptibility of Alzheimer's Disease. *See e.g.*, Braak E, et al., Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *Clin. Neuroscience* (1999) 249: 14-22. ("Alzheimer's disease is a relentlessly progressive dementing disorder which can be detected clinically only in its end phase." The illness remains subclinical for years, often several decades will elapse between the onset of histological lesions and evidence of clinical symptoms.)

As described in paragraphs 22-25 of the Rule 132 Declaration of Dr. Eugeen Vanmechelen, Appendix 3 is an extension of the Delcourte et al (2002) and Deramecourt et al. (2006) studies. Appendix 3 differs from prior studies presented in the Specification at Figure 7, Tables 6 and 8, in that, in addition to PHF-tau and Aβ staging, the patient samples are assessed for the presence of specific N-terminal truncated $A\beta_{42}$ peptides. These studies further indicate that there are two different populations of "controls." Those subjects highlighted in yellow represent normal aging "controls," whereas the remainder of the "control" patients in Table 1 of Appendix 3 are likely in early stages of AD (Id. at ¶¶ 26-28). Thus, detection of N-terminal truncated $A\beta_{42}$ peptides in samples from these subjects is significant in that it signals early stages

of AD. As shown in the specification and in Appendix 3, certain $A\beta_{42}$ variants are frequently detected in subjects with infraclinical AD. (Id. at ¶ 29) These and other N-terminal truncated $A\beta_{42}$ peptides are also detected in subjects with full blown AD. (Id. at ¶ 30). Identification of the N-terminal $A\beta_{42}$ variants in early stages of AD is significant because these variants are thought to initiate amyloid plaque formation/aggregation (Id. at ¶ 31). Determining the risk or susceptibility to AD in early stages may provide an opportunity mitigate or prevent further development of AD pathology.

Conclusion

Applicant believes that the rejections have been adequately addressed and overcome through amendment of the claims and the foregoing remarks. The Applicant does not believe that any other fees are due. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, the Commissioner is authorized to deduct said fees from Deposit Account No. 08-3038/**11362.0039.NPUS01**. Reconsideration of the application is respectfully requested. Applicant respectfully requests that the claims now be advanced to allowance.

Respectfully submitted,

Patricia A. Kammerer
Reg. No. 29,775
Attorney for Assignee
INNOGENETICS N.V.

Customer No. 23369
HOWREY LLP
1111 Louisiana, Suite 2500
Houston, Texas 77002
(713) 787 1400

Date: August 17, 2007